

Oncodesign: publication of an article presenting promising results for the treatment of stone man syndrome (FOP)

- ALK2 is a kinase that presents an activating mutation in more than 90% of patients suffering from stone man syndrome, very rare and incurable genetic disease
- ALK2 inhibitors resulting from Oncodesign's Nanocyclix[®] platform significantly inhibit osteogenic differentiation in patient-derived cells
- This publication validates the interest of the kinase research field, and Oncodesign's technology for the exploration of this area

Dijon, le 24 October 2019 at 6:00pm CEST – ONCODESIGN (ALONC – FR0011766229), a biopharmaceutical group specialized in precision medicine, has published an article in the Bone and Mineral Research journal presenting promising results of tests on ALK2 inhibitors resulting from its Nanocyclix[®] platform, as part of a collaborative international project to identify new treatments for stone man syndrome.

Stone man syndrome, also known as *Fibrodysplasia Ossificans Progressiva* (FOP), is a very rare and incurable genetic disease that affects one in every 2 million people on the planet¹. It causes soft tissue to turn slowly into bone, gradually limiting the mobility and independence of patients and reducing their life expectancy to 40 years on average.

ALK2² is a kinase that has been identified as presenting an activating mutation in more than 90% of patients suffering from stone man syndrome, through work done by Professor Frederick Kaplan at the University of Pennsylvania School of Medicine in the USA.

Using its Nanocyclix[®] platform, Oncodesign identified highly selective inhibitors of ALK2 and its mutated form. Work done in collaboration with Dr Alex Bullock (University of Oxford, UK) and Professor Peter ten Dijke (Leiden University Medical Center, Netherlands) shows significant inhibition of osteogenic differentiation/reprogramming in FOP patient-derived cells containing the mutation.

Their work also confirmed the way in which Oncodesign's molecules interact with ALK2, making it possible to refine a new set of compounds that have all the characteristics required to begin an *in vivo* preclinical proof of concept phase.

Professor Peter Ten Dijke said: *"This publication is the result of long term collaboration between Oncodesign and the Leiden University Medical Center in the field of stone man syndrome. Oncodesign compounds highlighted significant inhibition of the osteogenic differentiation in our phenotypic assay in addition to a pathway specificity we never observed with other small molecule compounds we evaluated. The evaluation of the pharmacological tool will confirm the potential of these molecules, which could bring high value therapeutic agent to patients. »*

Jan Hoflack, Ph.D., Oncodesign's Chief Scientific and Operating Officer, added: *"Our Nanocyclix[®] platform enabled us to identify some very powerful ALK2 inhibitors that seem to show specificity in relation to the mutated form of this kinase, which causes FOP. This characteristic of our molecules sets them apart from those of our rivals and is attracting potential partners. FOP, or stone man syndrome, is an extremely rare but terrible disease, which is why we want to push forward this program, currently at the advanced lead compound stage, in partnership with major industry players or patient associations."*

¹ Around 2,500 people in the world today, source: FOP France

² Activin receptor-like kinase 2

Article: Development of macrocycle kinase inhibitors for ALK2 using Fibrodysplasia ossificans progressiva-derived endothelial cells

Journal of Bone and Mineral Research - the paper will be published in the newspaper in the coming weeks, but is already available online: <https://doi.org/10.1002/jbm4.10230>

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Upcoming scientific events:

- EORTC in Boston, US, October 26-30
- Drug Discovery 2019 - Looking Back To The Future in Liverpool, UK, November 5-6
- EBF in Barcelona, Spain, November 20-22

About kinases and Nanocyclix® technology

Kinases are a family of enzymes that play an essential role in regulating most cell functions: proliferation, cell cycle progression, metabolism, survival/apoptosis, repair of damaged DNA, motility and microenvironment response.

Using its Nanocyclix® technology module, Oncodesign identifies macrocyclic molecules capable of inhibiting both known and unexplored kinases, in a powerful and specific way. The platform continuously assesses a wide range of inhibitors and kinases, and only the most promising inhibitor/target kinase combinations go forward for more in-depth investigation.

In this way, Oncodesign has developed a portfolio of projects showing major potential in the treatment of diseases showing major unmet medical need. The portfolio contains molecules that have already progressed to the clinical stage (a TEP tracer for a specific type of lung cancer) as well as those at a much earlier stage of development.

About stone man syndrome (Fibrodysplasia Ossificans Progressiva – FOP)

Stone man syndrome is a rare genetic disease that gradually turns muscle cells into bone (heterotopic ossification). The cause, identified in 2006 by the research group led by Professor Frederick Kaplan, is a monogenic mutation affecting the gene that codes for the ALK2 kinase (mainly R206H), leading to overactivation of the signaling pathway involved in osteogenesis in 97% of patients.

The first clinical signs are found in patients around the age of 4 or 5, through X-ray analysis. Patients see their condition deteriorate gradually until their posture becomes frozen around 18 years old, and their life expectancy is only 40 years on average. There is currently no available treatment and no type of surgery is capable of slowing new bone formation. Flare-ups are mainly caused by contusions, injuries, infections and various inflammatory conditions.

Source: IFOPA - www.ifopa.com

About ONCODESIGN: www.oncodesign.com

Founded over 20 years ago by Dr. Philippe Genne, the Company's CEO and Chairman, Oncodesign is a biopharmaceutical company dedicated to precision medicine. With its unique experience acquired by working with more than 600 clients, including the world's largest pharmaceutical companies, along with its comprehensive technological platform combining state-of-the-art medicinal chemistry, pharmacology, regulated bioanalysis, medical imaging and Artificial Intelligence, Oncodesign is able to predict and identify, at a very early stage, each molecule's therapeutic usefulness and potential to become an effective drug. Applied to kinase inhibitors, which represent a market estimated at over \$46 billion in 2016 and accounting for almost 25% of the pharmaceutical industry's R&D expenditure, Oncodesign's technology has already enabled the targeting of several promising molecules with substantial therapeutic potential, in oncology and elsewhere, along with partnerships with pharmaceutical groups such as Bristol-Myers Squibb. Oncodesign is based in Dijon, France, in the heart of the town's university and hospital hub, and within the Paris-Saclay cluster. Oncodesign has 232 employees and subsidiaries in Canada and the USA.

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